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RESEARCH NOTE

Deletion of 11q24.2-qter in a male child with cleft lip and palate: an atypical feature of Jacobsen syndrome

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Abstract. Jacobsen syndrome (JS) is caused by the terminal deletion at the long arm of chromosome 11. It is characterized by growth retardation, intellectual disability, facial dysmorphism, and other congenital abnormalities. The subband 11q24.1 has been confirmed to be the critical region for the typical features of JS. The patient in the current study is a 2-year-old male child with prominent craniofacial abnormalities and congenital heart disease. High-resolution single-nucleotide polymorphism arrays revealed breakage in chromosome 11q beginning at 11q24.2, with complete deletion of the distal portion. We collected all available reports describing patients with breakages at 11q24.1 or 11q24.2, and compared it with the typical features of JS. We found that the phenotype of cleft lip and palate (CLP) was present in both groups of patients with no overlap region in the deletion region (between 11q21-q23 and 11q24.2-qter), which indicated that other genes may be related to CLP in JS.

Keywords. Jacobsen syndrome; cleft lip and palate; congenital heart disease; copy number variation; 11q24 deletion.

Introduction

The first case of Jacobsen syndrome (JS) was described in 1973, in a family of three generations in which many members had inherited an unbalanced 11;21 translocation from their balanced translocation carrier parents (Jacobsen *et al.* 1973). The deletion region varies from 7 to 20 Mb, and the breakpoints usually began at 11q23.3, which extends to the distal end of 11q (Grossfeld *et al.* 2004). The severity of neurocognitive dysfunction in JS patients depends heavily on the precise location of the deletion region, and there are considerable individual differences in the clinical manifestations. In several cases, JS can be clinically diagnosed before the patient is one year old, and patients with mild clinical manifestations are evaluated by clinicians when they are older (Mattina *et al.* 2009).

The estimated incidence of JS is about one in 100,000, and the male/female ratio is 1:2 (Grossfeld *et al.* 2004). As per the current knowledge, the deletion region that determines the clinical manifestations of JS must be reduced to 700 kb or shorter in size, and the key genes are *ETS-1* and *FLI-1* (Conrad *et al.* 2019). Congenital chromoanasynthesis is another cause of JS. It is a complex rearrangement of chromosomes, and it can include deletions and duplications on chromosome 11 and microhomology signatures at the breakpoint (Anzick *et al.* 2020).

Cleft lip and palate (CLP) is an atypical feature of JS, and only six patients have been reported (Schinzel *et al.* 1977; Meyer *et al.* 2000; Serra *et al.* 2021). Among the six patients, four had overlapping deletion regions located at 11q21-11q23. The other two patients had the overlapping deleted region at 11q24.1-qter, which overlaps with the present patient.

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The present study shows that the patient has a 7-Mb deletion of chromosome 11q24.2, and he presented clinically with craniofacial abnormalities, intellectual disability, developmental delays, ventricular septal defects, and a CLP.

Materials and methods

Cytogenetic analysis

Peripheral blood was collected from the patient and from his parents. Chromosome analysis was performed using the standard procedure of G-banded techniques at a 550-band resolution level.

DNA extraction

Genomic DNA was extracted from the peripheral blood of the patient and his parents using a DNeasy Blood & Tissue kit (Qiagen, Valencia, USA) according to the extraction protocol.

SNParray analysis

The patient's genomic DNA sample was hybridized with the HumanOmni1-Quad Chip (Illumina). The Illumina BeadScan genotyping system (Beadstation Scanner 500; Illumina, San Diego, USA) was used to obtain signal intensities of SNP probes.

Editorial policies and ethical considerations

The study protocol was approved by the Review Board of the Second Xiangya Hospital of the Central South University in China, and the study participants or their parents or guardians provided informed consent.

Results

Case report

The patient is a 2-year-old male child, born at 39 weeks of gestation by cesarean section. His birth weight was 2840 g (< -1 SD), length was 47 cm (< -1 SD) and occipitofrontal head circumference was 34 cm. His 1 and 5 min Apgar scores was 6 and 8. He was the first child of two nonconsanguineous parents. The patient had no history of bleeding and no family history of any relevant abnormalities. On physical examination at 2 years of age, the patient presented with trigonocephaly, a high and prominent forehead, a flat nasal bridge, a short nose, hypertelorism and a heart murmur. His face was basically symmetrical from left to right, the left nostril was larger, the nasal base was concave, and the nasal columella was short. The uvula was dehiscent to the left anterior teeth area, and the alveolar ridge was dehiscent in full thickness, about 1.5 cm at its widest part (figure 1). His weight was 9.7 kg (< -2 SD), length was 82 cm (< -1 SD), occipitofrontal head circumference was 47 cm (< -1 SD). Transthoracic echocardiography showed a perimembranous ventricular septal defect. The patient had been treated with surgical repair of ventricular septal defect (VSD) at the age of 2 because of his growth retardation and recurrent upper respiratory tract infections. Psychomotor testing at 2 years and 5 months of age revealed a developmental age of 18 months, with a significant delay in language (evaluated at 17 months) and in gross and fine motor skills (18 and 22 months, respectively). Hematology results were within normal range (platelet count was 275,000/μL, PT, APTT, INR were 11.2s, 30.8s, 0.98, respectively). Neurological, audiological, and ophthalmological examinations results were normal.

CNV analysis

SNP-array analysis was performed on the patient to find out the chromosomal abnormality by using the Illumina HumanOmni1-Quad array. The analysis revealed the presence of a 7 Mb terminal deletion located at 11q24.2-qter, between 127,504,076 and 134,942,926 bp. According to the CNV result and typical clinical presentations, the patient was diagnosed with JS (figure 2).

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Discussion

Researchers speculated that the crucial band of JS is located at 11q24.1 (Fryns *et al.* 1986). We collected records of patients whose breakpoints were located at 11q24.1 or 11q24.2 and compared the typical features of JS (table 1 in electronic supplementary material at http://www.ias.ac.in/jgenet/). To the best of our knowledge, 26 patients have been reported with breakpoints located at 11q24.1 or 11q24.2. The most common clinical presentations in these regions were: developmental delays (19/26, 73.1%), short stature (18/26, 69.2%), congenital heart disease (CHD, 17/26, 65.4%), ocular hypertelorism (17/26, 65.4%), broad nasal bridge (14/26, 53.8%), limb abnormalities (14/26, 53.8%), intellectual disability (11/26, 42.3%), low-set ears (10/26, 38.5%), down slanting palpebral fissures (11/26, 42.3%), thrombocytopenia or pancytopenia (11/26, 42.3%). Less common clinical presentations included autism spectrum disorders (ASD), attention deficit hyperactivity disorder, neutropenia, osteoporosis, hypogammaglobulinaemia,

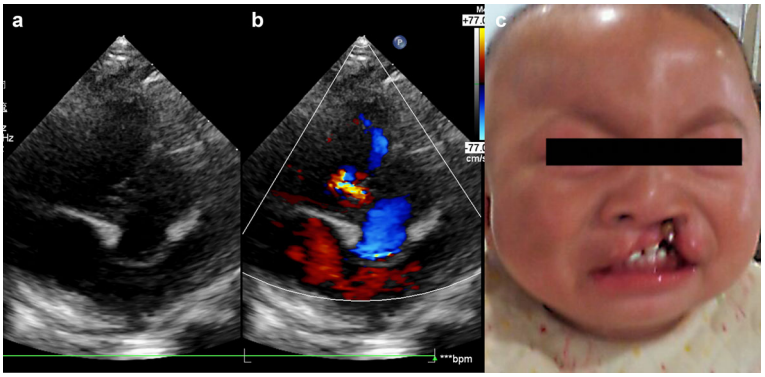

Figure 1. Facial abnormalities of the patient.

pectus carinatum, hearing loss, ophthalmic anomalies, and neurological abnormalities (table 1 in electronic supplementary material). The higher frequency of clinical phenotypes in the 26 patients were consistent with typical JS clinical phenotypes reported in the current literature (Grossfeld *et al.* 2004; Mattina *et al.* 2009). Of the 26 patients with deletion region starting at 11q24.1 or 24.2, there is one patient (11q24.1-qter) with occult submucous cleft palate and two patients with CLP (11q24.2-qter, 11q24.1-qter, respectively). All three patients presented with congenital heart disease, ocular hypertelorism and cleft palate. Among the higher frequent clinical phenotypes (>30.5%) summarized in 26 patients, the first patient had no developmental delay and short stature. The patient in this study had no thrombocytopenia and down slanting palpebral fissures.

ETS-1 has been proven to be the cause of CHD in JS patients. Heterozygous and homozygous *ETS-1* knock-out mice were produced against a C57/B6 background. Homozygous mice showed almost 100% penetrance of CHD (Ye *et al.* 2010). Located at 11q24.2-25, there are many genes associated with susceptibility to ASD, such as *NTM*, *KIRREL3* and *ARHGAP32*. The structure of the sub-cortical space and the volume of occipital gray matter were changed by the mutation of the *NTM* gene (Maruani *et al.* 2015). Akshoomoff *et al.* reported a patient with ASD who had a 243-kb deletion in the distal region of 11q, which overlapped the interstitial deletion of 11q in patients with typical features of JS and ASD as reported by Guerin *et al. KIRREL-3* and *ARHGAP32* are both associated with ASD (Akshoomoff *et al.* 2015; Guerin *et al.* 2012). However, the ASD patient in the former study with the small deletion region in the distal area of 11q did not contain *KIRREL-3*, which further supports the conclusion that *ARHGAP32* is associated with ASD. *ARHGAP32* affects synaptic plasticity by interacting with beta-catenin, which modulates the structure of the synapses and regulates their function (Nakamura *et al.* 2002).

CLP is a common congenital malformation. There are more than 200 genetic syndromes associated with cleft lip and 400 genetic carriers of cleft palate (Wong and Hagg 2004). The incidence of CLP in live births is approximately 1/700 and varies widely depending on the geographical origin, racial and ethnic group, environmental factors, and socioeconomic status (Worley *et al.* 2018). To the best of our knowledge, there are only four CLP and two submucous palatal cleft (SPC) patients with JS in the existing reports, and their deletion regions are 11q14.2-q23.2, 11q21-q23.1, 11q21-q23, 11q21-q23.1, and 11q24.1-q25 (two patients), respectively (Schinzel *et al.* 1977; Meyer *et al.* 2000; Serra *et al.* 2021). In patients with the common deletion region for 11q21-23, the genes associated with CLP were *MMP-1*, *MMP-3*, *MMP-13*, *MRE-11*, *ATM*, *AMOTL-1*. One of the reasons for the occurrence of CLP is that the unstable cross-linking between collagen fibres leads to the failure of the palatal matrix to elevate. *MMP-1* had proteolytic activity on collagens I, II, and III, while collagen III is abundant in mesenchymal cells of the embryonic palate, and collagen I is widely presented in the mesenchymal cells and epithelial cells of the embryonic palate. Therefore, when increased *MMP-1* transcription leads to increased degradation of collagen fibres, it may weaken the robustness of cross-linking, resulting in the failure of the palatal matrix to elevate and cause cleft palate (Pratt and King 1972; Hassel *et al.* 1976; D'Angelo *et al.* 1994). *MMP-3* is widely present in the morphogenesis of the palatal shelf, and is mainly distributed in the palatal mesenchyme after the fusion of the palatal shelf. It affects the fusion of the palatal shelf by regulating the transformation of the palatal epithelial to the palatal mesenchymal (Morris-Wiman *et al.* 2000; Letra *et al.* 2014). During the fusion of palatal shelf, *MMP-13* expressed both in medial edge epithelial and adjacent mesenchymal cell at the midline seam and completed epithelial to mesenchymal transformation by degrade the basement membrane proteins or extracellular matrix, which is an active role in palatogenesis (Blavier *et al.* 2001). *MRE11* recruits *ATM* to repair DNA damage at DNA double-strand breaks, and *ATM* activates DNA methyltransferases (DNMT1) that methylate specific regulatory regions including the *NOGGIN* promoter. As a BMP antagonist, *NOGGIN* is mainly expressed in the palatal epithelium in the early stage of palate development, and its overexpression will lead to the repression of BMP expression in the palatal epithelium, thereby affecting the

Figure 2. The results of CNV analysis. HumanOmni1-Quad Chip results of the deletion region (Chr11:127,504,076-134,942,926) in the proband. The middle panel shows the key annotated genes.

integrity of the palatal epithelium and normal palatogenesis (He *et al.* 2010). Rips *et al.* (2021) reported a patient with a CLP who exhibited a missense mutation in the *AMOTL1* gene. Overexpression of *AMOT1* results in the repression of WNT/β-catenin signalling, and this pathway is implicated in craniofacial development, palatal mesenchyme proliferation, primary lip and palate formation and fusion (Rips *et al.* 2021). In the present case, the patient's deletion region was 11q24.2-11q25, which did not overlap with any previously reported deletion regions except for the case 5 and case 6 (figure 3). *B3GAT1*, *ST14* and *ETS-1* are genes associated with CLP for the 11q24.2-qter region. GWAS has shown *B3GAT1* to be included in new recessive loci implicated in nonsyndromic cleft lip with or without cleft palate (NS CL/P) (Camargo *et al.* 2012). Hypomorphic mutations in the human *SPINT2* gene cause a wide range of abnormalities, including the cleft palate. During tissue morphogenesis, the main function of *SPINT2* is to inhibit the transmembrane serine protease matriptase encoded by *ST14* (Szabo *et al.* 2009). Cell cotransformation shows that *ETS-1* activates the promoter of *TBX22*, and a loss of function mutation in the promoter of *TBX22* located in the core-binding site of transcription factor *ETS-1* has been found in a six-generation family with cleft palate and hyper-nasal speech. EMSA and ChIP assays have indicated that the mutation disrupts the binding of *ETS-1*, which decreases the activity of *TBX22* and thus leads to cleft palate birth defects (Fu *et al.* 2015). In addition, although there is no research on *ETS-1* leading to cleft lip and palate by regulating *MMPs*, some studies have shown that *ETS-1* converted endothelial cells to angiogenic phenotype by upregulating *MMP-1*, *MMP-3* and *MMP-9* (Oda *et al.* 1999). Therefore, we speculate that the patients whose deletion region located at 11q21-q23 or 11q24.1-qter have a common mechanism for CLP by regulating the *MMPs*. This is probably a common but not the only mechanism for CLP in JS.

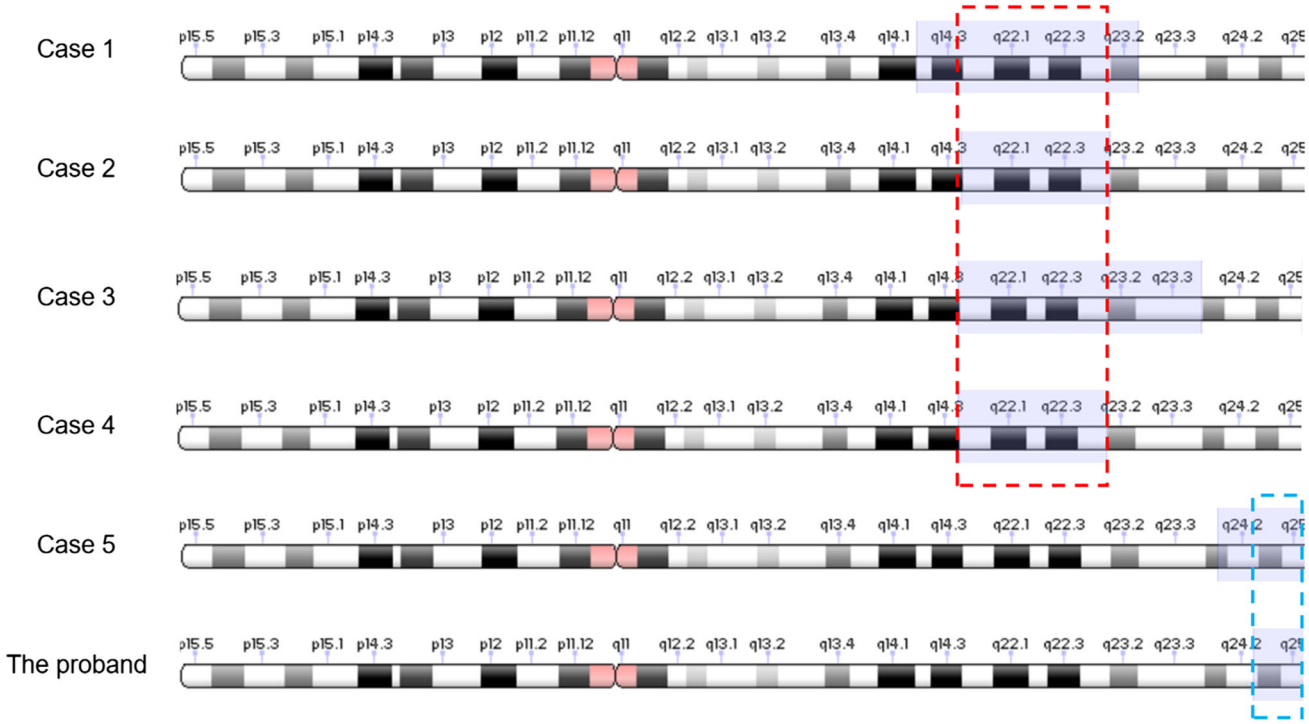

Figure 3. The deletion regions of patients. The deletion regions in case1, case2, case3, case4, case5, case6 and the proband are: 11q14.2-11q23.2, 11q21-11q23.1, 11q21-11q23, 11q21-11q23.1, 11q24.1-11q25, 11q24.2-11q25, respectively. The common deleted region at case1–4 is 11q21-q23 (the part enclosed by the red dashed line). The common deleted region at case5, case6 and the current patient is 11q24.2-q25 (the part enclosed by the blue dashed line). These figures were downloaded from NCBI genome database (https://www.ncbi.nlm.nih.gov/projects/genome/guide/human/index.shtml).

Among the patients whose breakpoints started at 11q24.1 or 11q24.2, only three had submucosal cleft palate or CLP. The incomplete penetrance of CLP suggested multi-gene regulation and epigenetic and environmental effects capable of suppressing the expression of CLP in patients with JS. In conclusion, the clinical presentation in the current patient and others with breakages starting at 11q24.1 or 11q24.2 is consistent with JS (table 1 in electronic supplementary material), indicating that the genes responsible for the symptoms of JS, including craniofacial abnormalities, cardiac defects, neural development, and renal/urinary tract anomalies are located in the 11q24.1-qter region. This is consistent with the findings of previous studies. However, the variable penetrance of these genes leads to different clinical manifestations in different patients. Of the 26 patients with breakages located at 11q24.1 or 11q24.2, only three had cleft palates (one submucosal cleft palate and two CLP), which means that multi-gene regulation, epigenetic factors, and environmental effects play a role in the development of CLP in JS.

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Authors' contributions

All authors made a significant contribution to the work reported. JDW collected the data and wrote the manuscript. TLZ, SJH, XYG and LYW conducted the treatment. ZPT made all necessary modifications to the manuscript. The final draft was read and approved by all authors.

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